Is a Pattern of Increasing Biomarker Concentrations Important for Long-Term Risk Stratification in Acute Coronary Syndrome Patients Presenting Early after the Onset of Symptoms?

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BACKGROUND: Guidelines for treatment of acute coronary syndrome (ACS) recommend observing a rise or fall in cardiac troponin (cTn) concentrations for assessing acute injury. It is unknown whether a rising pattern presages a more adverse long-term prognosis than elevations that do not change. The present study assessed whether a rising pattern of cardiac biomarkers was more prognostic than simple elevations.

METHODS: We measured N-terminal pro-brain natriuretic peptide (NT-proBNP) (Roche), cTnT (Roche) and cTnI (Beckman Coulter) in 212 ACS patients. These biomarkers were measured in coincident EDTA and heparin plasma samples available from at least 2 different time points, an early first specimen obtained within the median of 2 hours after onset of symptoms, interquartile range (IQR) 2–4 hours, and a later second specimen obtained at 9 hours, IQR 9–9 hours. The cTn concentration in the second specimen was used to classify myocardial necrosis (cTnI >0.04 ug/L; cTnT >0.01 ug/L). Outcomes [death, myocardial infarction (MI), heart failure (HF)] were obtained >8 years after the initial presentation. For patients with myocardial necrosis and a cTn concentration ratio (second/first measured concentrations) ≥1.00, the concentration ratios and the absolute concentrations in the second specimen were used to assess prognosis after 4 years.

RESULTS: In myocardial necrosis, the relative change (cTnI2/cTnI1) was greater for cTnI than for cTnT (P <0.01), whereas the relative change in NT-proBNP was the same regardless of which troponin was used to classify necrosis (P = 0.71). The concentration ratio for cTnI, cTnT, and NT-proBNP was not useful for risk stratification (i.e., death/MI/HF; P ≥0.15).

CONCLUSIONS: A rise in cardiac troponin or NT-proBNP concentration in ACS patients presenting early after onset of pain is not helpful for long-term prognosis.

Definitions and guidelines for the management of patients with acute myocardial infarction (AMI) have always referred to patterns of increasing and/or decreasing biomarker concentrations (1–5). It is unclear, however, whether defining an acute etiology on the basis of changing biomarker concentrations enhances the long-term prognostic effect of the detection of cardiac troponin (cTn) concentrations above the 99th percentile, because the mechanisms for these elevations may vary (6, 7). What is clear is that high cTn concentrations are prognostic for poor outcomes (8, 9). We conducted the present study to address this issue by investigating the prognostic value over time of the detection of relative increases in biomarkers (e.g., cTnI, cTnT, and NT-proBNP) in patients with myocardial necrosis (cTnI >99th percentile).

The study population and outcome analyses have been previously described (5, 9–14). Research ethics board approval was obtained to measure biomarkers in the stored samples and to make health outcome linkages (blinded to those who measured the biomarkers) to the Registered Persons Database for mortality outcomes, and the Canadian Institute for Health Information Discharge Abstract Database for hospital discharges associated with MI and heart failure (HF) (12). Briefly, all patients who presented to the emergency department with symptoms suggestive of cardiac ischemia (n = 448 assessed by triage staff in 1996) were included; however, for this substudy only those patients with coincident EDTA and heparin plasma samples available from at least 2 different time points were selected (n = 216 included; n = 232 excluded) (13).

The heparin specimens were measured in 2003 for cTnI (AccuTnI, second generation, Access®, Beckman Coulter) (5, 9, 10, 12), and the EDTA specimens, originally collected for creatinine-kinase MB isomform analysis, were measured in 2006 for cTnT (fourth generation) and N-terminal pro-brain natriuretic peptide (NT-proBNP) (Elecsys®, Roche) (13, 14).
able, designated as first specimen, obtained a median of 2 hours after onset of symptoms (interquartile range [IQR] 2–4 hours) and the second specimen, obtained closest to 9 hours after the onset of symptoms, (IQR: 9–9 hours). In the event that the first specimen was obtained >6 hours after symptom onset, then the next specimen obtained at least 3 hours later was selected as the second specimen. The minimum interval between specimen pairs was 3 hours, and the maximum was 12 hours [median (IQR) 6.5 (5–8) hours]. During the biomarker measurement phase, 4 patient samples had error codes for cTnT, and these patients were excluded, leaving samples from 212 patients available for analyses.

In separate assessments, the concentrations of cTnI and cTnT in the second specimen were used to classify patients as positive or negative for myocardial necrosis, using the 99th percentile for the AccuTnI second-generation assay and the lower limit of detection (LoD) for the cTnT fourth-generation assay, respectively (cTnI >0.04 ug/L, n = 83 patients; cTnT >0.01 ug/L, n = 88 patients; P = 0.3 by McNemar test) (15). The relative changes for cTnI, cTnT, and NT-proBNP were calculated as the ratios of the biomarker concentrations (biomarker<sub>2nd specimen</sub>/biomarker<sub>1st specimen</sub>). For this calculation, the concentrations at the lower limit of detection (LoD) were used for the AccuTnI second-generation assay (0.01 ug/L), cTnT fourth-generation (0.01 ug/L), and NT-proBNP (5 ng/L), when the reported concentrations were 0.00 ug/L for cTnI (n = 72 for the first specimen and n = 37 for the second specimen), <0.01 ug/L for cTnT (n = 152 for the first specimen and n = 116 for the second specimen), and <5 ng/L for NT-proBNP (n = 1 for the first specimen). These ratios and the absolute concentrations of the biomarkers in the second specimen were used for outcome analysis in the 81 (cTnI) and 85 (cTnT) patients who were assessed as having myocardial necrosis based on rising patterns of cTnI and cTnT, respectively. Patients with a falling pattern (cTn first concentration > cTn second concentration) were excluded from the outcome analysis (in total 2 patients for cTnI and 3 patients for cTnT were excluded; there was no patient overlap). Kaplan-Meier curves were constructed to display time to an event (death/MI/HF), with differences between groups (defined by quartiles for the relative rise indicators) assessed by the log-rank test. Between-group comparisons of central tendency were based on the Mann–Whitney and Wilcoxon signed-rank tests. Analyses were performed using SAS version 9.1.3 and GraphPad Prism version 5.00.

We have previously demonstrated in our ACS study population that absolute (i.e., peak) concentrations of cTnI, as determined by the AccuTnI assay, that are either below the 99th percentile (0.02–0.03 ug/L), or slightly above (0.04–0.10 ug/L, which includes measurements with less than the recommended precision, because the 10% CV limit is 0.06 ug/L for this assay) are nonetheless predictive of poor outcomes up to 8 years after the event (9, 12). In the present study, Kaplan-Meier analyses were performed separately using the cTnI or cTnT concentrations in the second specimen to assess outcomes (Fig. 1, A and B). Consistent with our previous findings in this population, patients with detectable cTnI (0.02–0.04 ug/L) and those with cTnI concentrations above the 99th percentile (>0.04 ug/L) showed clear differences in event-free survival (absence of death/MI) compared to those with no detectable cTnI (≤0.01 ug/L) (44%, 31%, and 65%, respectively, at 8 years post event; P < 0.001 with the >99th percentile group at higher risk compared to the detectable group; P = 0.014). For cTnT, the Kaplan-Meier analysis was performed using the second specimen cTnT concentrations in 3 groups, with cutoffs based on the LoD (0.01 ug/L) and the 10% CV concentration determined within the Hamilton Regional Laboratory Medicine program using the Bio-Rad Liquicheck<sup>TM</sup> Cardiac Markers Control LT-level low QC material (0.04 ug/L – total imprecision). The 3 groups with cTnT ≤0.010 ug/L (i.e., ≤LoD), 0.011–0.040 ug/L (detectable, with imprecision >10%), and >0.040 ug/L (high, with imprecision ≤10%) also displayed differences in event-free survival (62%, 31%, or 26%, respectively, at 8 years post event; P <0.001); however, there was no difference in risk between the detectable vs the high cTnT groups (P = 0.19).

Increases in biomarker concentrations in the 212 patients are shown in Table 1. Patients with myocardial necrosis (second specimen cTnI >99th percentile; second specimen cTnT >LoD) had higher median biomarker ratios (i.e., >1, indicating an overall relative increase) for all 3 markers, cTnI, cTnT, and NT-proBNP. Patients with myocardial necrosis also had higher absolute concentrations of NT-proBNP. Patients positive for necrosis as indicated by cTnI concentrations had, on average, a higher ratio (greater relative concentration change) than the patients with necrosis indicated by cTnT concentrations (P <0.001). The 2 troponin-positive groups showed no difference in NT-proBNP ratios (P = 0.71).

Kaplan-Meier analyses of the concentration ratios for cTnI, cTnT, and NT-proBNP were performed for patients with documented myocardial necrosis who had increasing cTn concentrations (cTnI, n = 81; cTnT, n = 85). For the second specimens, we performed quartile analysis of the association between concentration ratios and the absolute NT-proBNP concentration and patient event-free survival (i.e., absence of death/MI/HF) up to 4 years following presentation to assess the usefulness of these concentration...
measurements for predicting outcomes early after the event. There was no difference between the quartiles for the relative change for either cTnI \( (P = 0.73) \) or cTnT \( (P = 0.83) \) (see Fig. 1, C and D) nor for the relative change in NT-proBNP in either the cTn-positive group \( (P = 0.15) \) for the NT-proBNP ratio in the cTnI group and \( P = 0.31 \) for the NT-proBNP ratio in the cTnT group). The only analyses that approached significance in patients with increased troponin were for the absolute concentrations of NT-proBNP \( (P = 0.05 \) for cTnI and \( P = 0.06 \) for cTnT).

The detection of increases in cTn concentrations is diagnostically important for AMI, in that it documents that an acute evolving event is occurring. For long-term prognosis, however, observing an acute change in these biomarkers does not appear to be as informative. BNP and NT-proBNP have both been shown to provide prognostic information that is complementary to cTn \( (4) \). Of critical importance, however, are indications that for these biomarkers, even increased concentrations not associated with dynamic changes over time convey long-term prognostic information. Our study was not large enough to exclude differences in timing of outcome events that might differ between patients with a pattern of increases over time and those with potentially more chronic increases. This distinction may be of substantial clinical importance, because Newby et al. \( (16) \) reported in a much larger series that the data from additional measurements of cTnT performed 8 or 16 hours after baseline measurements contributed significantly to risk stratification for mortality at 30 days and 1 year. We also did not assess increasing troponin concentrations that remained below the 99th percentile (more sensitive troponin assays are required for this), and to operationalize this analysis, we set undetectable values at the LoD. If such patients are excluded from the analysis, the results are not altered (data not shown).

The data collection and analyses in our study are conceptually similar to those of Agewall et al. \( (17) \), who recently reported that increases of cTn concentrations in patients admitted to the coronary care unit have similar prognostic importance regardless of their apparent etiology. These data do not obviate the diag-
nostic importance of a rising pattern that may be indicative of an acute process and may influence short-term prognosis to a greater extent (16). However, they do reinforce the advocacy of follow-up of all patients with increased cTn concentrations, even when not deemed to be acute, as an essential component of patient care (18).

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References


Table 1. Concentration changes of cardiac troponin (cTnI and cTnT) and NT-proBNP in the ACS cohort (N = 212).a

<table>
<thead>
<tr>
<th>Variable, median (IQR)</th>
<th>Patients negative for necrosis</th>
<th>Patients positive for necrosisb</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnI (AccuTnI 2nd generation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. classified by cTnI (2nd)</td>
<td>129</td>
<td>83</td>
<td></td>
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<tr>
<td>Concentration of cTnI (2nd), ug/L</td>
<td>0.01 (0.01–0.02)</td>
<td>0.55 (0.15–6.62)</td>
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<tr>
<td>Time between specimens, h</td>
<td>6 (5–7)</td>
<td>7 (5–8)</td>
<td></td>
</tr>
<tr>
<td>Ratio cTnI (2nd/1st)</td>
<td>1.00 (1.00–1.75)</td>
<td>9.00 (1.80–37.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concentration of NT-proBNP (2nd), ng/L</td>
<td>134 (41–463)</td>
<td>450 (90–1839)</td>
<td>&lt;0.001</td>
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<td>Ratio NT-proBNP (2nd/1st)</td>
<td>1.00 (0.80–1.50)</td>
<td>1.40 (1.00–2.60)</td>
<td>0.001</td>
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<tr>
<td>cTnT (4th generation)</td>
<td></td>
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</tr>
<tr>
<td>No. classified by cTnT (2nd conc.)</td>
<td>124</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Concentration of cTnT (2nd), ug/L</td>
<td>0.01 (0.01–0.01)</td>
<td>0.13 (0.03–0.86)</td>
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<td>Time between specimens, h</td>
<td>6 (5–7)</td>
<td>7 (5–8)</td>
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<td>Ratio cTnT (2nd/1st)</td>
<td>1.00 (1.00–1.00)</td>
<td>3.10 (1.33–13.5)</td>
<td>&lt;0.001</td>
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<tr>
<td>Concentration of NT-proBNP (2nd), ng/L</td>
<td>100 (41–382)</td>
<td>569 (141–2184)</td>
<td>&lt;0.001</td>
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<tr>
<td>Ratio NT-proBNP (2nd/1st)</td>
<td>1.00 (0.80–1.50)</td>
<td>1.40 (1.00–2.58)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

a Values are presented as n or median (IQR).
b >0.04 μg/L.

a Values are presented as n or median (IQR).


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